Remarks

The Amendments

Claim 67 has been amended to recite that the amino acid sequence of the claimed serine racemase is at least "95%" identical to SEQ ID NO:8 or 10 and "comprises a pyridoxal 5′ binding region consisting of amino acids 47-60 of SEQ ID NO:8 or SEQ ID NO:10." Canceled claim 13 supports the recitation of 95% identity. The pyridoxal 5′ binding region is disclosed on page 5, line 30, to page 6, line 1: "The protein contains a pyridoxal 5′ phosphate binding region (ELFQKTGSFKIRGA, amino acids 47-60 of SEQ ID NO: 8), which supports the biochemical prediction that the serine racemase is a pyridoxal phosphate binding protein (Figures 4 and 5)." See also amino acids 47-60 of SEQ ID NO:10.

Claim 67 also has been amended to recite that "differences between the amino acid sequence of the serine racemase and SEQ ID NO:8 or SEQ ID NO:10 lie in conservative amino acid substitutions which do not abolish serine racemase activity." This amendment is supported on page 6, line 28, to page 7, line 1: "Mammalian serine racemase proteins, however produced, can contain alterations in amino acid sequence relative to the amino acid sequences encoded by SEQ ID NOS: 1, 2, 3, or 9 which do not affect the serine racemase activity of the protein. Guidance in determining which amino acid residues may be conservatively substituted, inserted, or deleted without abolishing serine racemase activity can be found using computer programs well known in the art, such as DNASTAR software."

Claim 86 has been amended to recite the characteristics of the encoded serine racemase discussed above. In addition, claim 86 has been amended to recite that the claimed

polynucleotide is at least "95%" identical to the nucleotide sequence shown in SEQ ID NO:1 or SEQ ID NO:9. Canceled claim 20 supports this amendment.

The dependencies of claim 52 and 59 have been corrected.

The amendments introduce no new matter. The amendments were not presented earlier because Applicants believed their previous response would put the claims in condition for allowance.

The Objections to the Claims

Claims 39, 47-50, and 58-66 are objected to because they recite "mammalian serine racemase." The claims have been amended to delete the term "mammalian."

Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 52 and 59 Under 35 U.S.C. § 112, second paragraph

Claims 52 and 59 stand rejected under 35 U.S.C. § 112, second paragraph, because of incorrect dependencies. Applicants respectfully traverse the rejection.

Claim 52 has been amended to recite dependency from claim 51, rather than canceled claim 10. Claim 59 has been amended to recite dependency from claim 58, rather than claim 56.

Applicants respectfully request withdrawal of the rejection.

The Rejections Under 35 U.S.C. § 112, first paragraph

Claims 67-97 stand rejected under 35 U.S.C. § 112, first paragraph, as insufficiently described in the specification and as not enabled. Claims 71, 72, 87, and 88 have been canceled. Applicants respectfully traverse the rejections of claims 67-70, 73-86, and 89-97.

Claims 67-70, 73-86, and 89-97 recite genera of isolated serine racemases that have the following structural and functional characteristics:

- an amino acid sequence that is at least 95% identical to SEQ ID NO:8 or SEQ ID NO:10 determined according to the Smith-Waterman homology search algorithm, using an affine gap search with gap open penalty of 12 and a gap extension penalty of 1;
- a pyridoxal 5′ phosphate binding region consisting of amino acids 47-60 of SEQ ID NO:8 or SEQ ID NO:10;
- an amino acid sequence that differs from SEQ ID NO:8 or SEQ ID NO:10 by conservative amino acid substitutions which do not abolish serine racemase activity; and
- a specific activity of at least 0.075 μmole L-serine/mg/hour;

Claims 77-82, 86, and 89-97 recite genera of polynucleotides that encode serine racemases having the structural and functional properties described above. The specification both describes and enables the recited genera.

1. Written Description

The first paragraph of 35 U.S.C. § 112 requires that the specification provide a written description of the claimed invention:

> [t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The purpose of the written description requirement is to ensure that the specification conveys to those skilled in the art that the applicants possessed the claimed subject matter as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). With respect to a claimed genus, the U.S. Patent and Trademark Office's Written Description Guidelines state:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by . . . disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus . . . .

66 Fed. Reg. 1099, 1106 (January 5, 2001), internal reference omitted, approved in *Enzo Biochem, Inc. v. Gen-Probe Incorporated*, 296 F.3d 1316, 1325, 63 U.S.P.Q.2d (BNA) 1609, 1613 (Fed. Cir. 2002). The specification describes a sufficient number of representative species having the recited structural and functional characteristics to describe the recited genera.

Each of the species within the recited genus of racemases recited in claims 67-70, 73-86, and 89-97 has common structural features. Each of the serine racemases encompassed within the recited genus has the following three structural features:

- a pyridoxal 5′ phosphate binding region consisting of amino acids 47-60 of SEQ ID NO:8 or SEQ ID NO:10;
- an amino acid sequence which is at least 95% identical to either SEQ ID NO:8 or SEQ ID NO:10, where percent identity is determined using a specifically recited algorithm (Smith-Waterman) with particular, recited parameters (using an affine gap search with gap open penalty of 12, gap extension penalty of 1); and
- an amino acid sequence which differs from SEQ ID NO:8 or SEQ ID NO:10 by conservative amino acid substitutions which do not abolish serine racemase activity.

The pyridoxal 5′ phosphate binding region has a recited amino acid sequence. The specification teaches that a pyridoxal 5′ phosphate binding region is correlated with the functional property of pyridoxal phosphate binding. See page 5, line 30, to page 6, line 1 of the specification. In addition, each of the serine racemases within the recited genus has the functional property of having a specific activity of at least 0.075 μmole L-serine/mg/hour.

The specification explicitly discloses two serine racemase proteins, comprising SEQ ID NOS:8 and 10, respectively. In light of the well-defined pyridoxal 5′ phosphate binding region, the high percentage amino acid sequence identity of the claimed serine racemases with SEQ ID NOS:8 or 10, and the recitation that differences between the amino acid sequences of the claimed

racemases and SEQ ID NOS:8 or 10 lie in conservative amino acid substitutions, these two species are representative of the recited genus of serine racemases.

The genus of polynucleotides recited in claims 77-82 encode the serine racemases recited in claim 67 and discussed above. Because of the well-known correlation between an amino acid sequence and the nucleotide sequences that can encode it (the genetic code), the specification also discloses to one skilled in the art this genus of polynucleotides. According to the genetic code there is a very precisely defined universe of nucleotide sequences that can encode any particular amino acid sequence. The known correlation between structure and the function of encoding is the well-known correlation between an amino acid and the three-nucleotide codons that encode that amino acid according to the genetic code. See the Written Description Guidelines, 66 Fed. Reg. at 1111, n. 57: "For example, in the molecular biology arts, if an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence."

Similarly, the specification also adequately describes the genus of polynucleotides recited in claims 86-97. Polynucleotides of this genus encode members of the genus of serine racemases discussed above and have nucleotide sequences which are at least 95% identical to SEQ ID NO:1 or SEQ ID NO:9 as determined according to the Smith-Waterman homology search algorithm, using an affine gap search with gap open penalty of 12 and a gap extension penalty of 1. Disclosure of SEQ ID NOS:1 and 9 together with the recited algorithm inherently describes all polynucleotides that are at least 95% (or 96, 97, 98, or 99%) identical to SEQ ID NOS:1 or 9.

The specification must be considered as a whole when determining whether the written description requirement is met. *In re Wright*, 866 F.2d 422, 425, 9 U.S.P.Q.2d (BNA) 1649,

1651 (Fed. Cir. 1989). The knowledge of one skilled in the art also must be considered, because the specification must "indicate[s] to persons skilled in the art that as of the [filing] date the applicant had invented what is now claimed." *All Dental Prodx LLC v. Advantage Dental Products Inc.*, 309 F.3d 774, 779, 64 U.S.P.Q.2d (BNA) 1945, 1948 (Fed. Cir. 2002). When read as a whole, taking into account the knowledge of persons skilled in the art at the January 19, 1999 priority date of the present application, this specification indicates to those skilled in the art that applicants invented the subject matter of claims 67-97 as of the application's January 19, 1999 priority date.

Applicants respectfully request withdrawal of the rejection.

2. Enablement

The proper standard by which to evaluate the scope of enablement that the specification provides for claims 67-70, 73-86, and 89-97 is whether any experimentation that may be needed to practice the claimed invention by the skilled artisan is undue or unreasonable. *In re Wands*, 858 F.2d 731, 736-37, 8 U.S.P.Q.2d (BNA) 1400, 1404 (Fed. Cir. 1988). The legal test for whether a disclosure provides adequate enablement for a generic claim is that "the scope of the claims must bear a *reasonable correlation* to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. (BNA) 18, 24 (C.C.P.A. 1970) (emphasis added). The present specification meets this standard and therefore enables preparations of serine racemase which have the recited properties.

The specification is addressed to those skilled in the art. The law is clear that the specification need not provide knowledge which is generally known by those skilled in the art; Applicants can properly rely on common knowledge in the art to bolster and supplement its

disclosure. *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986); *Genentech Inc. v. Novo Nordisk A/S,* 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997). The teachings in the specification, together with the knowledge and skill of those in the art at the January 19, 1999 priority date of this application, would guide one skilled in the art to which amino acids of SEQ ID NOS:8 or 10 could be conservatively altered to obtain a protein having an amino acid sequence which is at least 95% identical to SEQ ID NO:8 or 10 without abolishing serine racemase activity, as recited in independent claim 67. The Final Office Action acknowledges that "[t]here is no dispute that the Smith-Waterman and other algorithms and methods of altering a protein sequence and methods of screening for racemase activity were well known in the art at the time of the invention." Page 10, lines 11-13. The universe of amino acids that can be substituted conservatively is well defined in the art (*e.g.*, Val↔Ile↔Leu, Asp↔Glu, Lys↔Arg, Asn↔Gln, and Phe↔Trp). *See* Alberts *et al.*, eds., MOLECULAR BIOLOGY OF THE CELL, 1983, pages 58-59 (attached to the response filed December 29 and 30, 2003). Example 2 of the application teaches serine racemase assays. The specification also teaches the use of routine amino acid analysis techniques: "These techniques include, but are not limited to, hydrophobicity and hydrophilicity plots, homology searches for various motifs, antigenic indices, and standard algorithms such as those disclosed in Harlow & Lane, ANTIBODIES – A LABORATORY MANUAL (Cold Spring Harbor Laboratory, 1988)." Page 6, lines 9-12. The specification discloses the recited pyridoxal 5′ phosphate binding region (ELFQKTGSFKIRGA) on page 5, lines 30-31.

These teachings easily permit one skilled in the art to prepare serine racemase proteins with a pyridoxal 5′ phosphate binding region consisting of amino acids 47-60 of SEQ ID NO:8 or SEQ ID NO:10 and with an amino acid sequence that is at least 95% identical to SEQ ID NO:8 or 10 in which the differences lie in conservative amino acid substitutions. Dependent claims 73-76 recite an even greater percent identity to SEQ ID NOS:8 or 10 -- at least 96, 97, 98, or 99% identity with SEQ ID NO:8 or 10, respectively. Such proteins can easily be prepared; for example, a protein having at least 99% identity with SEQ ID NO:10, for example, would differ only in at most 3 amino acids (340 amino acids x 0.01). Once the substituted proteins were prepared, one skilled in the art could determine which of these proteins had the serine racemase activity recited in claim 67 or in dependent claims 68-70 merely by carrying out routine screening using the assays disclosed in the specification.

The polynucleotides recited in claims 77-80 encode the serine racemase proteins discussed above. Preparing such polynucleotides is a simple matter of applying the well-known genetic code to the amino acid sequences of these proteins. The polynucleotides recited in claims 86 and 89-97 encode the recited serine racemases and have nucleotide sequences at least 95% identical to SEQ ID NO:1 or 9 as determined by a particular, recited algorithm with specified parameters. As to these polynucleotides, the Final Office Action states that "[i]t is agreed that a highly homologous gene is enabled." Page 9, lines 16-17. Polynucleotides that encode the same recited genus of proteins and which are at least 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NOS:1 or 9 are highly homologous to the recited sequences. Thus, at a minimum the rejection should not apply to claims 77-82, 86, and 89-97.

The specification provides sufficient disclosure to enable one skilled in the art to make and use the polypeptides and polynucleotides recited in claims 67-70, 73-86, and 89-97 without recourse to undue experimentation. Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

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